main problems in vision to-day is the question of what the rods are doing under photopic conditions.

Conclusion

Enough has been said to indicate that the rigid trichromatic theory and the dogmatic assertion of the presence of three types of cone in the fovea of the normal eye are not entirely satisfactory. The study of specific retinal areas, functionally by the use of small fields, structurally by the use of reliable histological methods, and electrophysiologically in other animals, is now the obvious method of approach. Further work on the same lines with colour-blind subjects can almost be guaranteed to yield further dividends. In particular, a more enlightened approach to the evolution of visual mechanisms may well give clues on the nature of the mechanism for colour-vision : thus, there are many indications that the colour-sense may have arisen when a central apparatus was evolved for comparing and evaluating the information already reaching the brain through separate channels previously developed for other purposes—for example, for night and day vision, for increased visual acuity, etc. The time has now come, therefore, for a more biological and comparative approach to the subject. The working of the human eye cannot be treated in isolation as a purely physical or psychological problem ; it must be studied in relation to the evolutionary history of vision as a whole.

INFLUENCE OF ASCORBIC ACID ON THE HEALING OF CORNEAL ULCERS IN MAN

BY

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It is accepted that the repair of collagenous tissue is dependent on an adequate supply of ascorbic acid (Höjer, 1924 ; Menkin, Wolbach, and Menkin, 1934 ; Wolbach and Howe, 1926). Furthermore, ascorbic acid has been shown by Schmid and Bürki (1943), Henkes (1946), and Pirie (1946) to exist in a relatively high concentration in the cornea. The cornea is largely composed of collagen. It is, moreover, avascular. Thus vitamin C may play an unusually important part in the metabolism of this special tissue and possibly also in the resolution of corneal lesions.

Galloway, Garry, and Hitchin (1948), working with guinea-pigs, found that the healing of superficial injuries made with a dental burr and involving only the epithelium was not delayed even when the guinea-pigs were in a subscorbutic state. In their experiments, however, healing may have been effected predominantly by a sliding of epithelial cells from the corneal margin (Arey and Covode, 1943 ; Buschke, Friedenwald, and Fleischmann, 1943 ; Mann, 1944). In such injuries there was no occasion for new formation of collagen.

Campbell, Ferguson, and Garry (1950), using heat injuries to the epithelium alone in scorbutic guinea-pigs, confirmed the findings of Galloway, Garry, and Hitchin (1948) ; but they showed that deeper burns, involving the anterior two-thirds of the corneal stroma, took approximately 30% longer to heal in scorbutic guinea-pigs than in those fully saturated with ascorbic acid. Furthermore, even after epithelial healing was complete, structural weakness of the wound persisted for as long as three weeks after the injury in the scorbutic animals, while in the saturated guinea-pigs the strength of the cornea was restored in 11 days.

These results suggest that ascorbic acid may be of value in the treatment of human corneal lesions. In order to test this possibility we undertook the present investigation. Our study was restricted to the healing of small corneal ulcers in man so as to simulate the animal experiments conducted by Campbell, Ferguson, and Garry (1950). Suitable cases can readily be collected in sufficient numbers to justify statistical analysis.

Such an investigation on human beings can never hope to be so clear-cut as that on the guinea-pigs, in which the experimental group was reduced to a subscorbutic state and the control group had an ample intake of vitamin C. All our patients were eating a more or less normal diet, the intake of vitamin C probably reaching 50 mg. daily in some cases. Therefore, in order to produce blood levels in sufficient contrast with the group on a normal diet, we gave half our patients very massive doses of vitamin C.

Method

The patients studied in this investigation were in attendance at the out-patient department of the Glasgow Eye Infirmary between November, 1949, and March, 1950.

Approximately half the patients received 0.5 g. of ascorbic acid three times daily ; the remaining patients received control tablets containing no ascorbic acid, but of identical appearance and taste. Thus the patients in the principal group probably received 30 to 50 times as much ascorbic acid as the patients in the control group, who received ascorbic acid only in their diet. Administration was continued until healing was complete.

The clinical examination of the patients was carried out by one of us (T. A. S. B.), who throughout the experiment was unaware of the type of tablet administered to each patient.

A detailed clinical history was obtained from each patient. This was followed by a careful examination of the lesion, and such details as its size and position on the cornea were noted.

To assess the extent of the ulcer one drop of a 2% aqueous solution of sodium fluorescein was instilled into the conjunctival sac. After one minute exactly, excess fluorescein was washed off with a stream of isotonic sodium chloride solution delivered from a pipette. The intensity of fluorescence of the ulcer was then measured in a dark room by placing alongside the patient's eye a series of standard strips of filter paper impregnated with varying concentrations of sodium fluorescein. Fluorescence was induced by exposure to a mercury vapour lamp fitted with a Wood's glass screen, and situated about 2 feet (60 cm.) from the patient.

Our standard consisted of five strips, 1 by ½ in. (2.5 by 1.25 cm.), of No. 1 Whatman filter paper impregnated with fluorescein so that the intensity of fluorescence increased in approximately linear steps (Campbell and Boyd, 1950). Table I gives details of these standard strips.

As healing of a corneal ulcer progresses, the intensity of the fluorescence decreases and finally ceases when epithelization is complete. The time of healing was recorded as the interval between the first examination of the ulcer and the cessation of fluorescence. Observations were carried out daily.

TABLE I.—*Relation of the Concentration of Sodium Fluorescein to the Intensity of Fluorescence from the Standard Strips of Filter Paper for Clinical Use*

Intensity of Fluorescence	Concentration of Fluorescein in μg /cm.^{2} of Filter Paper
0	No fluorescein
1	0·5
2	1
3	2
4	4
5	8

Before the patient's final discharge the cornea was examined by slit-lamp and biomicroscope. The depth of the lesion was assessed by measuring the fraction of the thickness of the cornea now occupied by opacity.

Results

Analysis of the time taken for the corneal ulcers to epithelize showed that the mean healing time for the group of patients who had received ascorbic acid (22 cases) was 4 days, whereas for the control group (29 cases) the mean was 4.82 days. The difference, 0.82 days, is not significant. However, several factors which may have affected these times of healing were at work simultaneously. We therefore broke down our groups under the following headings.

1. Depth

The two groups above were further divided into subgroups of patients with "superficial" and with "deep" ulcers. Ulcers were considered to be "superficial" if, after healing, the residual opacity occupied a quarter or less of the corneal thickness as judged by slit-lamp and biomicroscope. The remainder were considered to be "deep."

Under normal circumstances one expects superficial ulcers to heal more rapidly than deep ulcers. This was indeed the case in the control group, in which the difference in healing time was highly significant (Table II, B D) ($P<0.0001$).

TABLE II.—*Relationship of Mean Healing Time to Depth of Corneal Ulcers*

Depth of Infiltration	Mean Healing Time in Days			
	Principals (Receiving 1·5 g. Additional Ascorbic Acid Daily)	No. of Cases	Controls (No Additional Ascorbic Acid)	No. of Cases
Superficial ..	$\overset{A}{3{\cdot}63\ (\pm 0{\cdot}54^*)}$	11	$\overset{B}{3{\cdot}80\ (\pm 0{\cdot}50)}$	15
Deep	$\overset{C}{4{\cdot}36\ (\pm 0{\cdot}40)}$	11	$\overset{D}{6{\cdot}15\ (\pm 0{\cdot}50)}$	13

* Standard error of mean.

In the group of patients receiving 1.5 g. of ascorbic acid daily the superficial ulcers also healed more rapidly than the deep ulcers, but this difference was not significant (Table II, A C). In other words, there is a suggestion here that depth of lesion has less effect upon the healing time when there is an abundant intake of ascorbic acid.

2. Ascorbic Acid

The difference between the mean healing times of the groups of patients with and without additional ascorbic acid is not significant in the case of superficial lesions (Table II, A B), but is significant in the case of deep lesions (Table II, C D) ($P<0.05$). This means that there is evidence that the administration of large doses of ascorbic acid does not influence the rate of healing of superficial ulcers, but that it does accelerate the healing of deep ulcers.

The significant difference between the time necessary for epithelization of "deep" ulcers in the principal and control groups is further substantiated by an examination of the course of healing in these two groups. Information on the course of healing was derived from daily estimation of the degree of fluorescence from each ulcer. In Fig. 1 the mean intensity of fluorescence on each day of observation has been plotted for the "deep" ulcers in the principal and control groups. Although by chance the group receiving ascorbic acid started with a higher degree of fluorescence, epithelial healing occurred rapidly, and so their "fluorescence gradient" was much steeper than that of the controls. In contrast, the "superficial" ulcers in principal and in control groups healed at similar rates (Fig. 2).

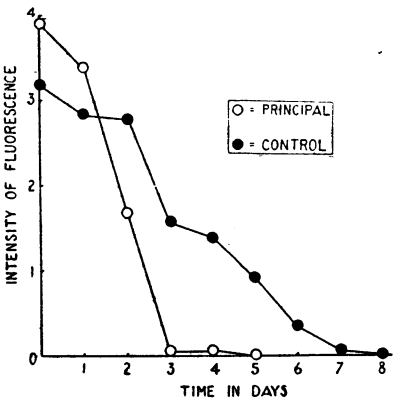

FIG. 1.—Mean intensity of fluorescence of deep corneal ulcers treated with (principals) and without ascorbic acid (controls) plotted for each day during healing. The figures on the ordinate correspond to the strip intensities described in the text.

It is thus clear that the course and time of healing were appreciably influenced by ascorbic acid only in deep ulcers; but can it be said that the deeper the lesion the more pronounced is the effect of ascorbic acid?

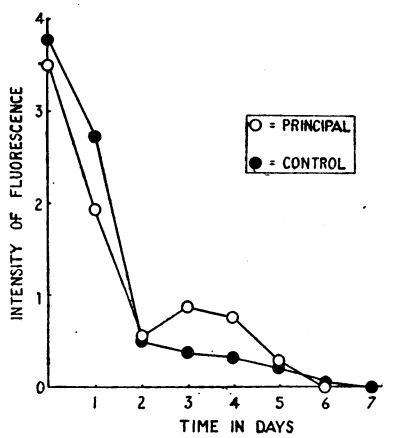

FIG. 2.—Mean intensity of fluorescence of superficial corneal ulcers treated with (principals) and without ascorbic acid (controls) plotted for each day during healing. The figures on the ordinate correspond to the strip intensities described in the text.

This question was investigated by a further subdivision of the deep and superficial groups. The deep group was broken down into a group in which the ulcers infiltrated one-half of the corneal thickness and another group affecting one-third. Similarly, the superficial group was divided into groups affecting one-quarter and one-fifth.

Fig. 3 shows diagrammatically the mean healing time of principals and controls in each of the four groups. The influence of depth upon the control groups is clearly shown by the progressive lengthening of healing time with increase of depth. There is a similar influence at work in the

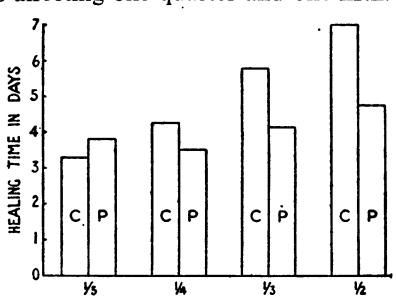

FIG. 3.—Mean healing time related to depth of infiltration in corneal ulcers treated with (P) and without ascorbic acid (C).

principal groups, but it is much less marked. It can thus be said that the deeper the lesion the more pronounced is the effect of ascorbic acid.

3. Site and Size

A priori, one might expect the area of the ulcers and their location on the cornea to have some effect on the rate of healing. We found only a slight tendency for central ulcers to heal more slowly than marginal ones, but analysis indicated that this difference could easily have arisen by chance.

As one would expect, the larger ulcers healed more slowly than the smaller ones, but the difference between the healing times of large and small ulcers in the series we examined was not significant. This was probably due to the comparatively small size of the ulcer diameters (0.25 to 2.5 mm.) in the cases included in this survey.

4. Local Therapy

All the cases received either gutt. sodium sulphacetamide 10% or gutt. penicillin 1,000 units per ml., three times daily; it was found that there was no significant difference between the healing times of sulphacetamide- and penicillin-treated cases. It is of interest, however, to note that, compared with sulphacetamide, penicillin significantly shortened the duration of conjunctival discharge.

5. Pyorrhoea

During the routine examination of our patients we noticed that a considerable number had pyorrhoea, and so decided to investigate its incidence. Pyorrhoea was said to be present only if the gums showed marked retraction with ulceration, or if pus could be expressed from the parodontal sulci.

Pyorrhoea occurred in these patients with corneal ulcers most frequently in the 20–40-year age group. Younger patients were usually free from infection, while many of the teeth of the older patients had been extracted. Since age appeared to affect the incidence of pyorrhoea, we collected a control group with the same age distribution from out-patients attending with non-infective ocular complaints and examined them for the presence of pyorrhoea.

Pyorrhoea was more common in the group with corneal ulceration (Table III). The χ^2 test showed that this difference in incidence was significant ($P<0.01$).

TABLE III.—*Incidence of Pyorrhoea in Patients Suffering from Corneal Ulcers Compared with a Control Group with Non-infective Eye Conditions*

	No. of Patients With Pyorrhoea	No. of Patients Without Pyorrhoea
Patients with ulcers	20 (69%)	9 (31%)
Patients without ulcers (control group)	8 (28%)	21 (72%)

$\chi^2 = 8{\cdot}4$. $P<0{\cdot}01$.

Discussion

Superficial Lesions of the Cornea

The absence of a significant effect of large doses of ascorbic acid on the healing times of superficial ulcers is in keeping with the results of Galloway, Garry, and Hitchin (1948), who inflicted mechanical wounds on the corneal epithelium, and of Campbell, Ferguson, and Garry (1950), who used thermal injuries. These workers considered that ascorbic acid is not required for a purely epithelial repair. The ulcers classified as superficial in the present series were not confined to the epithelium, but did involve a certain amount of stroma. The effect of this involvement of stroma on healing time appears to be masked in the superficial group. However, it becomes apparent when deep lesions are considered.

Deep Lesions of the Cornea

Large doses of ascorbic acid in man, however they act, do promote epithelization of deep corneal ulcers as judged by our fluorescein test. It may be that the slower rate of epithelization in the deep ulcers, where no addition of ascorbic acid had been given, was due to the absence of a suitable substratum of collagenous tissue. This is in keeping with the hypothesis of Hartwell (1929), who studied skin epithelization in cases of scurvy. This is not to say that there must be complete filling of the crater of the ulcer with collagenous tissue before the epithelium can spread across.

We can only conclude that in the patients receiving very large doses of ascorbic acid some changes had taken place in the exposed collagen of the bed of the ulcer to permit rapid overgrowth of the epithelium.

Action of Ascorbic Acid

The question now arises: "Why should massive doses of ascorbic acid accelerate the healing of corneal lesions in patients whose vitamin-C intake seemed normal?" We would like to stress that after careful questioning on dietary habits we found that there were very few patients who did not eat potatoes and vegetables daily. As no patient showed signs of scurvy it seems that this intake was sufficient for normal purposes, but our findings suggest that it was not optimum for the healing of corneal lesions. We therefore suggest that ascorbic acid, in such massive doses as 1.5 g. daily, has a value in therapy apart from its normal role as a vitamin at accepted levels of intake.

The nature of this action remains obscure at present. It may well be that there is a local deficiency at the site of any collagenous tissue lesion. If this be so, then benefit would accrue from the increased rate of diffusion which would arise from a temporary increase in the blood level of ascorbic acid. Moreover, in the case of avascular cornea this accelerated diffusion would tend to be of greater value than in vascular granulation tissue surrounding lesions elsewhere.

It is of interest to note that Campbell and Ferguson (1950) found that during the healing of heat injuries in subscorbutic guinea-pigs there was a greater tendency to corneal vascularization than in control animals with an adequate intake of ascorbic acid. The stimulus for this neo-vascularization may have been the increased metabolism of the healing tissue. It is possible that the guinea-pigs were unable to satisfy this increased demand from their reduced levels of ascorbic acid.

The original object of this study was to investigate whether the conclusions drawn by Campbell, Ferguson, and Garry (1950) from experiments on guinea-pigs could be applied to human beings. Therefore the study was restricted to small ulcers of a type which would be expected to heal with the usual treatment within a week or 10 days. It is unnecessary, of course, to give ascorbic acid normally to cases of this type. Our findings, however, greatly strengthen the clinical reports of Lyle and McLean (1941), and of Summers (1946), who reported on the effect of massive doses of ascorbic acid on a variety of serious corneal conditions.

We now feel that our results justify a critical study of a carefully controlled series of some of the graver but less common corneal conditions.

Summary

Fifty-one cases of small acute corneal ulcers were examined, and healing time ascertained by instillation of sodium fluorescein under standard arbitrary conditions.

Approximately half the patients received 1.5 g. of ascorbic acid daily; the remainder were given control tablets.

Deep ulcers healed significantly more slowly than superficial ulcers.

The administration of large doses of ascorbic acid had no significant effect upon the healing time of superficial ulcers, but significantly accelerated the healing of deep ulcers.

It is suggested that there may be a localized area around the site of regenerating corneal collagen where the ascorbic acid level falls below the optimum for rapid healing. Raising the general ascorbic acid level with massive doses increases the local rate of replacement.

Pyorrhoea occurred significantly more frequently in patients with corneal ulcers than in others with non-infective eye complaints.

We wish to thank Drs. J. Pendleton White, J. Hill, A. Wright Thomson, and A. Mellick, of the Glasgow Eye Infirmary, for permission to examine their patients. We also wish to express our gratitude to Professor R. C. Garry and Dr. J. B. deV. Weir for their kindly criticism and encouragement. We are indebted to Roche Products Ltd. for a liberal supply of control tablets and of tablets of ascorbic acid, and to the Rankin Medical Research Fund of the University of Glasgow for defraying the cost of this investigation.

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Courses of instruction on medical aspects of atomic warfare at the Royal Naval Medical School, originally started for medical officers of the Royal Navy, have been made available to wardmaster officers in the Royal Navy, to medical officers of the R.N.V.R., and to certain civilian members of the nursing profession. These courses were started in 1948. At first they were intended only for Naval medical officers, but soon it was decided that medical officers of the R.A.M.C. and R.A.F. should attend. In January, 1949, the doors were thrown open to civilian medical officers nominated by the Ministry of Health. The medical officers' standard course lasts five and a half days, and the subjects dealt with include atomic physics, effects of radiation in the human body, monitoring and defence organization, and treatment of casualties. The lectures are supplemented by films. Early this year shorter courses lasting three days for nursing officers of the three fighting Services were started, and these were also opened to members of the civilian nursing profession nominated by the Ministry of Health. In August the Admiralty decided that it was desirable that medical officers of the R.N.V.R. should be given an opportunity of attending similar courses of instruction, and these started in September. About the same time it was decided that dental officers of the R.N. and R.N.V.R., who, especially in wartime, play an important part in all medical defence organizations, should attend these short courses. There is a permanent staff of lecturers at the Royal Naval Medical School, and in addition lectures are given on special subjects by outside lecturers.

INTRAPERITONEAL INTESTINAL ANASTOMOSIS IN COLECTOMY

BY

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Below is presented a short series of 15 cases of strictures and ulcers of the colon (mostly carcinomas) treated by excision with intraperitoneal end-to-end anastomosis, both with and without colostomy.

A good deal has been written about these methods in the American literature from 1942 onwards, representative papers being those of Stone and McLanahan (1942), Wangensteen (1945), Waugh and Custer (1945), and Lahey (1946). In the British literature, however, there is a singular dearth of information on this subject in the last eight years—that is, since the new chemotherapeutic agents have altered the principles of colon surgery.

It is probable, therefore, that the extraperitoneal methods of Paul and Mikulicz are still in vogue up and down the country in cases that would be eminently suitable for an intraperitoneal method. I would at once agree that the latter method requires a certain standard of surgical skill in making an anastomosis, especially in accurate mucosal apposition, but where this exists I suggest that the end-to-end anastomosis is a much better procedure mechanically. Risk does not seem to be great in reasonably selected cases. It can, of course, be a good deal more radical than an extraperitoneal excision.

In contrast it might be said that a good deal of trouble can be associated with the extraperitoneal methods, not always reflected in textbooks and writings on the subject. Every practical surgeon will know how difficult it can be to get satisfactory crushing of a spur because of the interposition of painful mesenteric structures or the repeated slipping of the enterotome. An extraperitoneal closure in the presence of a partially crushed spur is always difficult and unsatisfactory, and may leave some degree of stricture. At all events, a colon firmly fixed to the abdominal wall can hardly function as well as a mobile colon in its correct anatomical position and with a properly constructed end-to-end anastomosis. So long as the risks of the two procedures were so different these facts were of no account; but now I believe that the difference in risk is slight in selected cases, and these facts should be given full weight in any decision on the correct line of treatment in a particular case.

The period in hospital for a primary colectomy need be no longer than for any other "clean stitch" case—approximately 14 days. If a colostomy has been done this will add another two weeks; the stay should therefore seldom exceed a month. Many a patient subjected to an extraperitoneal method will have been in hospital a good deal longer than this, and probably has had to undergo multiple attempts at spur-crushing and colostomy closure. This inevitably leads to a serious loss in his earnings as the weeks go by.

Selection of Suitable Cases

I wish to exclude rectosigmoid lesions from this discussion, as I have had no experience in these primary anastomoses, but there seems to be no good reason why any lesion of the colon should not be resectable by this method at one operation or be made resectable after the establishment of a simple colostomy to overcome the acute